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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,807	07/06/2006	David Paul Humphreys	CELL-0307	6569

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,807	HUMPHREYS ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *19-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/30/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 8 and 27-29 have been amended.

2. Claims 19-26 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-18 and 27-30 are under consideration.

4. This Office Action contains New Grounds of Rejections.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 30 April 2008 is acknowledged, however, the references cited therein are duplicate citations of the references listed on the PTO-892 mailed 05 March 2008 and hence the references listed on the IDS filed 30 April 2008 have been crossed-out. The references listed on the PTO-892 mailed 05 March 2008 have been fully considered by the examiner. Applicants' cooperation is requested in reviewing the file for duplicate citations in order to avoid delays at the time of issue.

Objections/Rejections Withdrawn

6. The requirement to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 because claims 12 and 14 are drawn to sequences (i.e., SEQ ID numbers), however, the instant application does not contain a sequence listing is withdrawn in view of the sequence listing filed 7/7/08.

7. The objection to the specification as not containing a reference to the prior application(s) as the first sentence(s) of the specification or in an application data sheet is withdrawn in view of the amendments to the specification filed 7/7/08.

8. The rejection of claims 1-7, 10-11, 12-13, 15-18, 27-28 and 30 under 35 U.S.C. 102(b) as being anticipated by Carter P. J. (WO 93/06217, 4/1/1993) as evidenced by Rodrigues et al (The Journal of Immunology, 151(12), 6954-6961,

December 15, 1993, IDS reference 20 filed 10/10/06) and Bodmer et al (WO 89/01974, 3/9/1989) is withdrawn in view of the amendments to the claims.

9. The rejection of claims 8-9 under 35 U.S.C. 102(b) as being anticipated by Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 43 filed 10/10/06) as evidenced by Rodrigues et al (The Journal of Immunology, 151(12), 6954-6961, December 15, 1993, IDS reference 20 filed 10/10/06) is withdrawn in view of the amendments to the claims.

Rejections Maintained

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. The rejection of claims 1-7, 10-18 and 27-30 under 35 U.S.C. 102(b) as being anticipated by Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 43 filed 10/10/06) as evidenced by Rodrigues et al (The Journal of Immunology, 151(12), 6954-6961, December 15, 1993, IDS reference 20 filed 10/10/06) is maintained.

The response filed 7/7/2008 states that Humphreys is concerned with the production of antibody fragments, particularly dimeric F()ab')2 fragments containing the hinge sequence TCPPCPXYCPPCPA as well as PEGylation of such fragments. Thus, the overriding emphasis in Humphreys is on antibody fragments with a hinge sequence containing four cysteines. Applicant also argues that Humphreys teaches in the examples, non-PEGylated Fab' fragments in which the interchain cysteines have been replaced with serines and in which

the hinge sequences contain one or two cysteines. Applicant states that these fragments are included purely as experimental comparators for the fragments containing four cysteines which are the unequivocal subject of the invention described in Humphreys. Applicants' arguments have been fully considered but are not found persuasive. Applicants' arguments that Humphreys is concerned with particularly dimeric F(ab')2 fragments containing the hinge sequence TCPPCPXYCPPCPA as well as PEGylation of such fragments and that Humphreys et al never produced PEGylated Fab' fragments containing only one or two cysteines in the hinge region are acknowledged, however, applicant is reminded that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005). Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi,* 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). The fact that Humphreys et al places particular emphasis or preference on certain disclosed embodiments does not overcome the fact that Humphreys et al also teach antibody fragments comprising a Fab or Fab' wherein the interchain cysteines of the CL and CH1 have been mutated to serines and Humphreys teaches various hinge peptides comprising one, or two or more cysteines (e.g., sequences identical to SEQ ID Nos:1-3) for the attachment of effector molecules, including polyethyleneglycol (PEG) (e.g., see entire document, particularly Table II, pp. 3-6, 8-11 and Examples).

Thus, Humphreys anticipates the claims as evidenced by Rodriguez et al and the rejection is maintained.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. The rejection of claims 1-7, 10, 15-18 and 27-30 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 43 filed 10/10/06) is maintained.

The response filed 7/7/08 states that one skilled in the art would not have attempted to attached PEG (or a derivative) to the hinge region of Fab' fragments containing only one or two cysteines in the hinge because of the risk that the PEG would draw water away from the antibody fragment, creating destabilizing effect on the fragment that would force the heavy and light chains apart. Applicant states that the fact that corresponding Fab' fragments were not PEGylated in the Humphreys reference would only have served to add to these

reservations and make the skilled artisan even more cautious, such that Humphreys is teaching one skilled in the art away from the present invention.

Applicant also states that the inventors discovered that, surprisingly, and contrary to prior perceptions in the art, the present inventors were able to demonstrate that even when an antibody Fab' fragment lacking the interchain disulfide is PEGylated, the heavy and light chain remain associated with each other and the PEGylated antibody Fab' fragment has equivalent antigen binding and *in vivo* activity compared to PEGylated Fab' fragments in which the interchain disulphide bond is present. Applicants' arguments have been fully considered but are not found persuasive. Applicants' arguments questioning the operability of the prior art, i.e., that PEGylation in the hinge region would destabilize the antibody fragment and force the heavy and light chains apart, and applicants' allegations of the surprising and unexpected discovery that an antibody fragment lacking the interchain cysteines can be provided with PEG effector molecules, and the heavy and light chains remain associated with each other, such that the PEGylated antibody Fab' fragment has equivalent antigen binding and *in vivo* activity compared to PEGylated Fab' fragments in which the interchain disulphide bond is present are acknowledged, however, applicant is reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter

from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). See MPEP 716.01(c).

Regarding the motivation to modify the Fab and Fab' fragments of claims 7 and 10 of U.S. Patent No. 6,642,356 B1, Humphreys teach Fab and Fab' fragments in which the interchain cysteines of the C_H1 and CL are substituted with serine and the hinge sequence TCPPCPXYCPPCPA, identical to the hinge sequence of claims 7 and 10 of U.S. Patent No. 6,642,356 B1, is used for the attachment of one or more PEG molecules, which increase serum permanence, reduce immunogenicity and decrease proteolysis *in vivo*. Thus, Humphreys et al teach that PEGylation of the hinge sequence TCPPCPXYCPPCPA provides the advantages of increased serum permanence, reduce immunogenicity and decreased proteolysis *in vivo.* The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Humphreys teaches that removal of the interchain disulfide bond does not affect stability (see pg. 12). Applicant is reminded that obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Furthermore, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed..." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a Fab or Fab'

fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the C_H1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for immunodiagnosis or immunotherapy in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Humphreys and the rejection is maintained.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1-18, 27-28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-18, 27-28 and 30 are indefinite in the recitation “derivative” in claims 1 and 27 as the exact meaning of the word is not known. The term “derivative” is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this term is the absence of an ascertainable meaning for said phrase. Since it is unclear the nature, direction and extent that the PEG molecules are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said term. In absence of a defined art recognized meaning for the term and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al (Analytical Biochemistry, 304(2):147-156, May 15, 2002, citied on PTO-892 mailed 3/5/08) in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 42 filed 10/10/06) and Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 43 filed 10/10/06).

Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that

are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and selenol-catalyzed reduction of disulfide bonds in Fab fragments has previously been reported (see entire document, particularly abstract, pp, 148, 154-155 and Fig. 1). Singh et al do not specifically teach an antibody comprising a Fab' fragment comprising a hinge region containing one or two cysteines and wherein the Fab' fragment has been modified by attachment of at least one PEG or PEG derivative wherein both the interchain cysteine of CL and the interchain cysteine of CH1 have been replaced with another amino acid such that the heavy chain in the fragment is not covalently bonded to the light chain. These deficiencies are made for in the teachings of Hesi et al and Humphreys.

Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 (e.g., antibody fragment comprising Fab') fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules, and wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and the PEG molecules are attached via a cysteine residue or residues engineered into a selected site or selected sites in the antibody fragment as well as pharmaceutical compositions comprising the anti-IL-8 antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer (see entire document, particularly pp. 20, lines 29-37, pp. 21-27, 37-38, 42, 98-102 and 104-105).

Humphreys teach Fab' fragments wherein the interchain cysteines of the CL and CH1 have been mutated to serines and Fab' hinge region peptides comprising one or two cysteines that efficiently generate dimers (e.g., di-Fab'), which are highly resistant to chemical reduction *in vivo* and the hinge peptides are well tolerated in *E.coli* and are non-immunogenic and the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or

more effector molecules, including polyethylene glycol may be attached (see entire document, particularly pp. 3-6, 8-11 and Examples and Table II).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprise a modified hinge region containing one or two cysteines as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides as taught by Singh et al as well as pharmaceutical compositions comprising said anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments and a pharmaceutically acceptable carrier, excipient or stabilizer for therapeutic benefit of inflammatory disorders.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprise a modified hinge region containing one or two cysteines as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides as taught by Singh et al as well as pharmaceutical compositions comprising said anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments and a pharmaceutically acceptable carrier, excipient or stabilizer for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys because Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable

homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 (e.g., antibody fragment comprising Fab') fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules, and wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and the PEG molecules are attached via a cysteine residue or residues engineered into a selected site or selected sites in the antibody fragment as well as pharmaceutical compositions comprising the anti-IL-8 antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer and Humphreys teach Fab' fragments wherein the interchain cysteines of the CL and CH1 have been mutated to serines and Fab' hinge region peptides comprising one or two cysteines that efficiently generate dimers (e.g., di-Fab'), which are highly resistant to chemical reduction *in vivo* and the hinge peptides are well tolerated in *E.coli* and are non-immunogenic and the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or more effector molecules, including polyethylene glycol may be attached. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments lacking the CL-CH1 interchain disulfide and comprising a hinge peptide containing one or two cysteines as well as a cysteine residues engineered into selected sites in the antibody fragment (e.g., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides as taught by Singh et al since selenol-catalyzed reduction of interchain disulfides provides a rapid method in which the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity. The

strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Singh et al provides evidence that reduction of interchain disulfide bonds of an antibody does not result in a significant decrease in affinity or stability and selenol-catalyzed reduction of disulfide bonds in Fab fragments has been performed previously (Singh et al, pg. 148 1st col.). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprise a modified hinge region containing one or two cysteines as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides as taught by Singh et al as well as pharmaceutical compositions comprising said anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments and a pharmaceutically acceptable carrier, excipient or stabilizer for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. No claim is allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**.

See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643